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SEARCH REQUEST FORM

Scientific and Technical Informati n Center

Requester's Full Name: Steven Tizio Examiner #: 79032 Date: 5/8/02
Art Unit: 1627 Phone Number 30 5-1903 Serial Number: 09/712,921
Mail Box and Bldg/Room Location: [redacted] Results Format Preferred (circle): PAPER DISK E-MAIL
3804

If m re than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: See attached

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Elected Invention: Claims 1-6

Search Claim 1 & Claim 2

Jan Delaval
Reference Librarian
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CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

****

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Searcher: Jan
Searcher Phone #: 4498
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PTO-1590 (8-01)

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STRUCTURE FILE UPDATES:   13 MAY 2002  HIGHEST RN 415678-09-0
DICTIONARY FILE UPDATES:  13 MAY 2002  HIGHEST RN 415678-09-0

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

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Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can l2

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   154531-34-7  REGISTRY
CN   Epidermal growth factor-like growth factor, heparin-binding (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   Heparin-binding EGF-like growth factor
CN   Heparin-binding epidermal growth factor-like growth factor
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
             372 REFERENCES IN FILE CA (1967 TO DATE)
               8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             377 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  136:307603

REFERENCE   2:  136:289048

REFERENCE   3:  136:276473

REFERENCE   4:  136:263211

REFERENCE   5:  136:256739

REFERENCE   6:  136:245262

REFERENCE   7:  136:241594

REFERENCE   8:  136:226829

REFERENCE   9:  136:214468

REFERENCE  10:  136:214305


=> d his
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Jan Delaval
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CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

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     (FILE 'HOME' ENTERED AT 14:13:19 ON 14 MAY 2002)
           SET COST OFF

     FILE 'HCAPLUS' ENTERED AT 14:13:33 ON 14 MAY 2002
L1           67 S ?HBEGF?

     FILE 'REGISTRY' ENTERED AT 14:13:56 ON 14 MAY 2002
L2            1 S 154531-34-7

     FILE 'HCAPLUS' ENTERED AT 14:14:38 ON 14 MAY 2002
L3          375 S L2
L4          517 S HEPARIN(L)BIND?(L)(EGF OR EPIDERMAL GROWTH FACTOR)(L)LIKE(L)G
L5          389 S HB EGF
L6          601 S L1,L3-L5
L7         9063 S GREEN(L)?FLUORESC?(L)PROTEIN OR GFP
L8            1 S L6 AND L7
L9            9 S ?FLUORESC?(L)PROTEIN AND L6
L10           1 S GREEN(L)?FLUORESC? AND L6
L11           8 S L9,L10 NOT L8
L12        1364 S IRES OR INTERNAL?(L)RIBOSOM?(L)ENTRY?(L)SITE
L13       17084 S (IL OR INTERLEUKIN)()4
L14       31932 S (IL OR INTERLEUKIN)(L)4
L15           1 S L6 AND L12
L16           8 S L6 AND L13
L17          11 S L6 AND L14
L18           1 S L15-L17 AND EPSILON
L19           1 S L8,L10,L15,L18
L20          18 S L8-L11,L15-L19 NOT L19
L21          11 S L20 AND (RECOMBIN? OR ?DIPHTHER? OR ?TOXIN? OR ?TOXOID? OR VE
L22           7 S L20 NOT L21
              E KINSELLA T/AU
L23           8 S E14,E15
L24           1 S L23 AND L6
L25           1 S L19,L24
              E RIGEL/PA,CS
L26           1 S E3-E13 AND L6
L27           1 S L25,L26
L28           1 S L27 AND L1,L2-L27
L29           0 S LL20-L22 NOT L28
L30          18 S L20-L22,L11 NOT L28
L31          18 S L30 AND L1,L2-L30

     FILE 'REGISTRY' ENTERED AT 14:44:55 ON 14 MAY 2002

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FILE 'HCAPLUS' ENTERED AT 14:45:09 ON 14 MAY 2002
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FILE COVERS 1907 - 14 May 2002  VOL 136 ISS 20
FILE LAST UPDATED: 12 May 2002  (20020512/ED)
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This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d l28 all

L28 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:360179 HCAPLUS
DN 134:361341
TI Reporter gene systems for screening for regulators of **interleukin 4**-induced immunoglobulin E synthesis
IN **Kinsella, Todd M.**
PA **Rigel Pharmaceuticals, Inc., USA**
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-12
ICS C12N015-62; C07K014-435; C07K014-475; C12N015-86; C12Q001-68; G01N033-50; G01N033-533
CC 1-1 (Pharmacology)
Section cross-reference(s): 3, 4, 10, 15
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001034806	A2	20010517	WO 2000-US31232	20001113
WO 2001034806	A3	20011129		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-165189P P 19991112
AB The invention relates to methods and compns. utilizing diphtheria toxin for screening purposes. The invention is particularly useful in screening for modulators of IgE synthesis, secretion and switch rearrangement. In particular methods of using diphtheria toxin induction of IgE gene expression by activation of the germline .**epsilon**. promoter via **heparin-binding epidermal growth factor-like growth factor** are described. Constructs that can use survival of Fas-induced apoptosis as a screening mechanism are described.
ST IgE synthesis regulation drug screening; **interleukin 4** inducible promoter effector drug screening; diphtheria toxin IgE gene expression induction effector screening
IT Animal cell line
(BJAB, expression host for screening for effectors of IgE gene expression; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)
IT Animal cell line
(CA-46, expression host for screening for effectors of IgE gene expression; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)
IT Enzymes, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA-recombining, class-switching, screening for; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Immunoglobulins
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(E; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**IRES** (**internal ribosomal entry site**) element, expression vector using; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Recombination, genetic
(Ig class switching, of IgE genes, screening for effectors of; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Apoptosis
(as selection mechanism in drug screening; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Toxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(diphtheria, as inducer of IgE gene expression, screening for modulators; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Drug screening
(for effectors of IgE biosynthesis; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT **Proteins**, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**green fluorescent**, variants, as reporter; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Reporter gene
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(in screening for effectors of IgE gene expression; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Allergy inhibitors
(inhibitors of IgE synthesis as, screening for; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Molecular cloning
(of IgE switch recombinases, reporter gene assay for; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT Secretion (process)
(protein, of IgE, screening for effectors of; reporter gene systems for screening for regulators of **interleukin 4**-induced IgE synthesis)

IT **Interleukin 4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(regulation of IgE synthesis by; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT Retroviral vectors
(reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT Fas antigen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(resistance to induction of apoptosis by, as selection mechanism in drug screening; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT Peptide library
(screening of, for effectors of IgE biosynthesis; reporter gene systems for screening for regulators of **interleukin** 4 -induced IgE synthesis)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.**epsilon**., screening for modulators of gene expression from; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT **154531-34-7D, Heparin-binding epidermal growth factor-like growth factor,** fusion **proteins** with **green fluorescent protein**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(as reporter; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT 339606-53-0, 1: PN: WO0134806 FIG: 1 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

IT 250382-52-6, 2: PN: WO9958663 FIG: 2B unclaimed DNA 339606-54-1 339606-55-2 339606-56-3 339606-57-4 339606-58-5 339606-59-6
RL: PRP (Properties)
(unclaimed sequence; reporter gene systems for screening for regulators of **interleukin** 4-induced IgE synthesis)

=> d l31 bib abs hitrn tot

L31 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:350757 HCAPLUS
TI Comparison of gene expression profiles in human keratinocyte mono-layer cultures, reconstituted epidermis and normal human skin; transcriptional effects of retinoid treatments in reconstituted human epidermis
AU Bernard, Francois-Xavier; Pedretti, Nathalie; Rosdy, Martin; Deguercy, Alain
CS BIOalternatives, Gencay, 86160, Fr.
SO Experimental Dermatology (2002), 11(1), 59-74
CODEN: EXDEEY; ISSN: 0906-6705
PB Blackwell Munksgaard
DT Journal
LA English
AB In order to validate a model for predictive **screening** of dermatol. drugs, we used a customized cDNA macro-array system contg. 475 skin-related genes to analyze the gene expression patterns in human keratinocytes from different origins: (1) normal human epidermal keratinocyte mono-layer cultures, (2) the com. available SkinEthic reconstituted human epidermis model, and (3) biopsies of normal human

epidermis. Few markers of those that were detected significantly in keratinocyte mono-layers or in reconstituted epidermis were undetected or detected at very low level in the normal epidermis biopsies. A comparative expression of more than 100 markers could be evidenced in both normal epidermis and reconstituted epidermis samples; however, only 90% of these were detected in keratinocyte monolayers: expression of several terminal differentiation markers, such as filaggrin, loricrin, and corneodesmosin were strongly detected in normal epidermis and reconstituted epidermis, but were not significantly expressed in keratinocyte mono-layers. Under the exptl. conditions described herein, the reconstituted human epidermis model was found to significantly reproduce the gene expression profile of normal human epidermis. Using the same methodol., we then investigated the effects of all-trans retinoic acid, 9-cis retinoic acid, all-trans retinol and a commercialized tretinoin-contg. cream (Retacnyl) on the gene expression profiles of reconstituted human epidermis. According to the nature and the length of the treatments, more than 40 genes were found significantly modified. Among the genes whose expression was decreased, we found cytokeratins 1, 10, 2E, and 6B, several cornified envelope precursors, integrins .alpha.3, .alpha.6, .beta.1, .beta.**4**, some components of desmosomes, of hemi-desmosomes and of the epidermal basement membrane. Transcriptional upregulation was obsd. for keratins 18 and 19, autocrine and paracrine growth factors such as **HB-EGF**, IGF 1, PDGF-A, calgranulins A and B, **interleukin**-1.alpha. and the other **IL**-1-related markers, type II **IL**-1 receptor and type I **IL**-1-receptor antagonist. Our results confirm most of the known effects of retinoids on human epidermis, but also give new insights into their complex pharmacol. activity on skin. The reconstituted human epidermis used proves to be a highly predictive model for efficacy evaluation of skin-targeted compds., such as retinoids.

L31 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:123358 HCAPLUS
DN 136:177962
TI Novel human kruppel-like factor 6 (KLF6) with tumor suppressor activity, and uses for diagnostics, therapeutics, and drug **screening**
IN Friedman, Scott; Li, Dan; Narla, Goutham; Martignetti, John; Heath, Karen
PA Mount Sinai School of Medicine, USA
SO PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002012894	A1	20020214	WO 2001-US25046	20010809

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-224111P P 20000809
AB The present invention is based on the identification of KLF6 as a tumor suppressor gene, and on the discovery that this gene was inactivated or altered in cancers. The inventors first showed that KLF6 is rapidly up-regulated in hepatocytes following partial hepatectomy in both wild type and p53 null animals. The inventors then examd. human tumors in which the p53 gene was intact, to det. if KLF6 gene was inactivated or if expression of the KLF6 protein was altered. The inventors confirmed that

KLF6 expression is attenuated in a variety of glial tumor cell lines. These findings were completed by loss of heterozygosity (LOH) studies. This invention provides a way to find addnl. mutations in the KLF6 gene that alter the activity of the protein in a variety of cancers, such as prostate colon, breast,ovarian, head and neck cancer, hepatocellular carcinoma, and lung cancer. The present invention relates to identification of KLF6, and to related diagnostic and therapeutic compns. and methods. The discovery of this tumor suppressor activity provides **screening** targets as well, particularly **screening** for compds. that overcome gene inactivation or alteration.

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:51533 HCAPLUS
DN 136:117381
TI Bifunctional antibody fusion proteins for targeted gene delivery
IN Nemerow, Glen R.; Li, Erguang
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; The Scripps Research Institute
SO PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002004522	A2	20020117	WO 2001-EP7878	20010709

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-613017 A 20000710
AB The authors disclose methods and products for targeting delivery **vectors**, such as adenoviral gene delivery particles, to selected cell types. The targeting is effected by a bifunctional mol. that specifically complexes with (1) a protein on the **vector** particle surface and (2) a cell surface proteins. In one example, the authors demonstrate improved adenovirus **vector** binding, internalization, and transgene gene expression in targeted melanoma cells using a fusion protein of tumor necrosis factor-.alpha. and an anti-penton base monoclonal antibody. Virus internalization and reporter gene expression was dependent on activation of phosphatidylinositol 3' kinase via the tumor necrosis factor receptor signaling pathway.
IT **154531-34-7D, Heparin-binding EGF-like growth factor,** fusion products
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with anti-genetic **vector** antibodies for enhanced gene delivery)

L31 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:855179 HCAPLUS
DN 136:260423
TI Gene Expression Analysis in Human Monocytes, Monocyte-Derived Dendritic Cells, and .alpha.-Galactosylceramide-Pulsed Monocyte-Derived Dendritic Cells
AU Lapteva, Natalia; Nieda, Mie; Ando, Yoshitaka; Nicol, Andrew; Ide, Kazuki; Yamaura, Ayako; Hatta-Ohashi, Yoko; Egawa, Kohji; Juji, Takeo; Tokunaga,

Kátsushi
.CS Department of Human Genetics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
SO Biochemical and Biophysical Research Communications (2001), 289(2), 531-538
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB In vitro proliferation and functional activation of V.alpha.24NKT cells following stimulation with .alpha.-galactosylceramide (.alpha.-GalCer)-pulsed dendritic cells (DCs) have been obsd. Because little is known about the mol. events on DCs following interaction with .alpha.-GalCer, we performed gene expression profiling of 2400 genes in monocytes and monocyte-derived immature DCs pulsed with .alpha.-GalCer (.alpha.-GalCer-imDCs). Overall, the expression levels of 48 genes were up-regulated and 28 were down-regulated in .alpha.-GalCer-imDCs. Semiquant. RT-PCR anal. on monocytes, imDCs, .alpha.-GalCer-imDCs, and mature DCs confirmed the up- and down-regulation of the mRNA expression levels of 28 selected genes. Notably, we identified the specific up-regulation of mRNA expression levels of RNase A and collapsin response mediator protein upon the stimulation of imDC with .alpha.-GalCer, suggesting a novel immunomodulating effect of .alpha.-GalCer on imDCs. In this study, we used imDCs prepd. by culturing of monocytes with GM-CSF and **IL-4** for 5 days and mDCs prepd. by further culturing of imDCs with TNF.alpha. for two extra days. (c) 2001 Academic Press.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:136138 HCAPLUS
DN 135:90999
TI **HB-EGF** is produced in the peritoneal cavity and enhances mesothelial cell adhesion and migration
AU Faull, Randall J.; Stanley, Jodie M.; Fraser, Scott; Power, David A.; Leavesley, David I.
CS Renal Laboratory, Royal Adelaide Hospital, Adelaide, Australia
SO Kidney International (2001), 59(2), 614-624
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
AB The mesothelial cell monolayer lining the peritoneal membrane needs const. repair in response to peritonitis and to the toxicity of peritoneal dialyzate. In many continuous ambulatory peritoneal dialysis (CAPD) patients, the repair process progressively fails, and membrane dysfunction and fibrosis occur. **Heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**) has an important role in wound repair and is also fibrogenic, and thus may be involved in these processes in the peritoneal cavity. The presence of **HB-EGF**, its receptors, and its assocd. **proteins** was detd. in peritoneal membrane biopsies, cultured human peritoneal mesothelial cells (HPMCs), and peritoneal macrophages from CAPD patients by reverse transcription-polymerase chain reaction, flow cytometry, and **immunofluorescence** immunocytochem. with confocal microscopy. **HB-EGF** effects on HPMC adhesion were measured by a static adhesion assay, on integrin expression by flow cytometry, and on migration by wound healing and chemotaxis assays. **HB-EGF**, its receptors HER-1 and HER-4, and the assocd. **proteins** CD9, CD44, and integrin .alpha.3.beta.1 were expressed by HPMCs and peritoneal macrophages. **HB-EGF** colocalized with HER-1 and HER-4 in HPMCs and induced their adhesion to collagen type

1,, expression of .beta.1 integrins, and migration. **HB-EGF** is produced by cells in the peritoneal cavity of CAPD patients and has functional effects on HPMCs that would facilitate repair of the mesothelial layer.

IT **154531-34-7, Heparin-binding epidermal growth factor-like growth factor**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**heparin-binding epidermal growth factor-like growth factor** formation in peritoneal cavity and enhances mesothelial cell adhesion and migration in dialysis wound repair)

RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:795994 HCAPLUS
DN 132:31744
TI Gene probes used for genetic profiling in healthcare **screening** and planning
IN Roberts, Gareth Wyn
PA Genostic Pharma Ltd., UK
SO PCT Int. Appl., 745 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9964627	A2	19991216	WO 1999-GB1780	19990604

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI	GB 1998-12099	A	19980606
	GB 1998-13291	A	19980620
	GB 1998-13611	A	19980624
	GB 1998-13835	A	19980627
	GB 1998-14110	A	19980701
	GB 1998-14580	A	19980707
	GB 1998-15438	A	19980716
	GB 1998-15574	A	19980718
	GB 1998-15576	A	19980718
	GB 1998-16085	A	19980724
	GB 1998-16086.	A	19980724
	GB 1998-16921	A	19980805
	GB 1998-17097	A	19980807
	GB 1998-17200	A	19980808
	GB 1998-17632	A	19980814
	GB 1998-17943	A	19980819

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice

and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

IT **154531-34-7**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare **screening** and planning)

L31 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:795993 HCAPLUS
DN 132:31743
TI Gene probes used for genetic profiling in healthcare **screening** and planning
IN Roberts, Gareth Wyn
PA Genostic Pharma Limited, UK
SO PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9964626	A2	19991216	WO 1999-GB1779	19990604
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9941586	A1	19991230	AU 1999-41586	19990604
	AU 9941587	A1	19991230	AU 1999-41587	19990604
	GB 2339200	A1	20000119	GB 1999-12914	19990604
	GB 2339200	B2	20010912		
	EP 1084273	A1	20010321	EP 1999-925207	19990604
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	GB 1998-12098	A	19980606		
	GB 1998-28289	A	19981223		
	GB 1998-16086	A	19980724		
	GB 1998-16921	A	19980805		

GB 1998-17097 A 19980807
GB 1998-17200 A 19980808
GB 1998-17632 A 19980814
GB 1998-17943 A 19980819
WO 1999-GB1779 W 19990604

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

IT **154531-34-7**
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(core group of disease-related genes; gene probes used for genetic profiling in healthcare **screening** and planning)

L31 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:735387 HCAPLUS
DN 132:192872
TI **Heparin-binding EGF-like growth factor** is expressed by mesangial cells and is involved in mesangial proliferation in glomerulonephritis
AU Takemura, Tsukasa; Murata, Yuka; Hino, Satoshi; Okada, Mitsuru; Yanagida, Hidehiko; Ikeda, Masaru; Yoshioka, Kazuo
CS Department of Pediatrics, Kinki University School of Medicine 377-2 Ohno-higashi, Osaka, 589-8511, Japan
SO Journal of Pathology (1999), 189(3), 431-438
CODEN: JPTLAS; ISSN: 0022-3417
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB **Heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**), a new member of the **EGF** family, is mitogenic for several types of cells, through **binding** to cell surface heparan sulfate proteoglycans. This study has attempted to delineate **HB-EGF** expression by mesangial cells and to identify its role in exptl. and human glomerulonephritis. Rat mesangial cells, cultured in the presence of phorbol acetate, hydrogen peroxide, interleukin-1.beta., and tumor necrosis **factor**-.alpha., expressed **HB-EGF** mRNA. **Recombinant HB-EGF** stimulated rat mesangial cells to proliferate and to express types I and III collagen. In the rat anti-Thy-1.1 nephritis, glomerular **HB-EGF** mRNA was up-regulated and peaked at days 5-7; its expression at the **protein** level in the glomerulus was prominent at days 5-10. By **immunofluorescence, HB -EGF** was pos. predominantly in the mesangial area of renal tissues from 23 of 45 patients with various types of human glomerulonephritis, showing a significant correlation with the grade of mesangial proliferation; there was no staining in tissues from patients with minimal change nephrotic syndrome and normal kidney tissues. These

data provide the evidence that **HB-EGF** is synthesized and expressed by mesangial cells and stimulates mesangial cell proliferation and collagen synthesis in vitro. **HB-EGF** is a potential mediator in mesangial cell proliferation and matrix expansion in exptl. and human glomerulonephritis.

IT **154531-34-7, Heparin-binding EGF-like growth factor**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**HB-EGF** expression in mesangium in relation to mesangial proliferation in glomerulonephritis)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:404856 HCAPLUS
DN 131:63507
TI Methods and compositions for improving the success of cell transplantation in a host
IN Tremblay, Jacques P.
PA Universite Laval, Can.
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9930730	A1	19990624	WO 1998-CA1176	19981215
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9918649	A1	19990705	AU 1999-18649	19981215
PRAI	CA 1997-2224768		19971215		
	CA 1997-2225837		19971224		
	WO 1998-CA1176		19981215		

AB The present invention covers significant improvements for each event involved in the transplantation success or graft survival. These improvements, sep. or combined with each other, greatly ameliorate the recovery of a tissue towards a normal function. They comprise: (a) the redn. of early death of transplanted cells by anti-inflammatory agents such as TGFbeta1, an inhibitor of oligosaccharide synthesis, a glucosidase, **IL**-10, vIL-10, **IL-4**, INFgamma, **IL**-2R, **IL**-1Ra, Fas-L, sCR1, a super oxide dismutase, a neutrophil inhibitory factor (NIF), a ligand binding in an antagonist fashion to LFA-1, MAC-1, ICAM-1, CD-18, CD-31, CD-50, E-selectin, P-selectin, TNFalpha, **IL**-1 and **IL**-8. The anti-inflammatory agents may comprise an anti-LFA-1 or -ICAM-1; (b) the improvement of the diffusion and of the fusion of transplanted cells with the host tissue by metalloproteases; (c) the ex vivo proliferation of the transplanted cells with growth factors or oncogenes; (d) the use of fibroblasts or stem cells in lieu of myoblasts, by transforming the formers into the latter with myogenic genes; (e) expressing utrophin in lieu of dystrophin in cases of muscular dystrophy; and (f) immunosuppressing the host for long-term graft survival.

IT **154531-34-7, Heparin binding epidermal**

growth factor like growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(anti-inflammatory compns. for improving the success of cell transplantation in a host)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:66673 HCAPLUS
DN 130:295965
TI Dietary .omega.3, .omega.-6, and .omega.-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes; a randomized volunteer study
AU Baumann, Klaus H.; Hessel, Franz; Larass, Iris; Muller, Thomas; Angerer, Peter; Kiefl, Rosemarie; von Schacky, Clemens
CS Medizinische Klinik, Klinikum Innenstadt, University of Munich, Munich, D-80336, Germany
SO Arteriosclerosis, Thrombosis, and Vascular Biology (1999), 19(1), 59-66
CODEN: ATVBFA; ISSN: 1079-5642
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Dietary .omega.-3 fatty acids retard coronary atherosclerosis. Previously, we demonstrated that dietary .omega.-3 fatty acids reduce platelet-derived growth factor (PDGF)-A and PDGF-B mRNA levels in unstimulated, human mononuclear cells (MNCs). In a randomized, investigator-blinded intervention trial, we have now compared the effect of ingestion of 7 g/d .omega.-3, .omega.-6, or .omega.-9 fatty acids for **4** wk vs. no dietary intervention on PDGF-A, PDGF-B, heparin-bound epidermal growth factor (**HB-EGF**), monocyte chemoattractant protein-1 (MCP-1), and **interleukin**-10 gene expression in unstimulated MNCs and in monocytes that were adherence-activated ex vivo in a total of 28 volunteers. In unstimulated MNCs, mRNA steady-state levels of PDGF-A, PDGF-B, and MCP-1 were reduced by 25.+-.10%, 31.+-.13%, and 40.+-.14%, resp., after .omega.-3 fatty acid ingestion, as assessed by quant. polymerase chain reaction (all $P<0.05$). In monocytes that were adherence-activated ex vivo for **4** and 20 h, mRNA steady-state levels of PDGF-A, PDGF-B, and MCP-1 were reduced by 25.+-.13%, 20.+-.15%, and 30.+-.8%, resp. (all $P<0.05$). **Interleukin**-10 and **HB-EGF** mRNA steady-state levels were not influenced by .omega.-3 fatty acid ingestion. Expression of all resp. mRNAs in control volunteers or in those ingesting .omega.-6 or .omega.-9 fatty acids were not altered. We conclude that human gene expression for PDGF-A, PDGF-B, and MCP-1, factors thought relevant to atherosclerosis, is constitutive, is const., and can be reduced only by dietary .omega.-3 fatty acids in unstimulated and adherence-activated monocytes.
IT **154531-34-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(dietary .omega.3, .omega.-6, and .omega.-9 unsatd. fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes; a randomized volunteer study)
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:33144 HCAPLUS
DN 128:136827

TI Immunohistochemical localization of **heparin-binding epidermal growth factor-like growth factor** in normal skin and skin cancers
AU Downing, Marc T.; Brigstock, David R.; Luquette, Mark H.; Crissman-Combs, Missy; Besner, Gail E.
CS Department of Surgery, The Ohio State University and Children's Hospital, Columbus, OH, 43205, USA
SO Histochem. J. (1997), 29(10), 735-744
CODEN: HISJAE; ISSN: 0018-2214
PB Chapman & Hall
DT Journal
LA English
AB **Heparin-binding epidermal growth factor (EGF)-like growth factor** is a 22-kDa glycoprotein that was originally identified as a secreted product of cultured human macrophages. Although the **growth factor** mRNA has been identified in various cells and tissues, the tissue distribution of the **protein** itself has rarely been demonstrated. In this study, the **EGF-like growth factor** was detected immunohistochem. in a variety of human skin samples by indirect **immunofluorescence** using a polyclonal rabbit antiserum raised against residues 26-41 of mature **heparin-binding EGF**. The keratinocytes of a variety of epithelium-derived structures demonstrated reproducible, specific staining for the **EGF**. In normal tissues, this staining was prominent in the basal cells of the epidermis and in the epithelial cells lining epidermal appendages such as hair follicles, sebaceous sweat glands and eccrine sweat glands. In addn., specific staining was detected in skin cancers derived from the basal epithelial cell layer, including basal and squamous cell carcinomas of the skin, with no staining detected in melanoma specimens. Immunoreactive **heparin-binding EGF** was characteristically assocd. with the surface of cells. With minor exceptions, the immunoreactive sites are identical to the known **EGF** receptor distribution in the skin, and suggest that keratinocyte-derived **heparin-binding EGF** may act in concert with other **EGF** family members in processes such as skin morphogenesis and wound repair, as well as in the development of skin cancers.
IT **154531-34-7, Heparin-binding epidermal growth factor-like growth factor**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(immunohistochem. localization of **heparin-binding epidermal growth factor-like growth factor** in normal skin and skin cancers)

L31 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:476819 HCAPLUS
DN 127:189113
TI Selective induction of **heparin-binding epidermal growth factor-like growth factor** by methylglyoxal and 3-deoxyglucosone in rat aortic smooth muscle cells. The involvement of reactive oxygen species formation and a possible implication for atherogenesis in diabetes
AU Che, Wenyi; Asahi, Michio; Takahashi, Motoko; Kaneto, Hideaki; Okado, Ayako; Higashiyama, Shigeki; Taniguchi, Naoyuki
CS Department of Biochemistry, Osaka University Medical School, Osaka, 565, Japan
SO J. Biol. Chem. (1997), 272(29), 18453-18459
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal

LA English
AB Methylglyoxal (MG) and 3-deoxyglucosone (3-DG), reactive dicarbonyl metabolites in the glyoxalase system and glycation reaction, resp., selectively induced **heparin-binding epidermal growth factor (HB-EGF)-like growth factor** mRNA in a dose- and time-dependent manner in rat aortic smooth muscle cells (RASMC). A nuclear run-on assay revealed that the dicarbonyl may regulate expression of **HB-EGF** at the transcription level. The dicarbonyl also increased the secretion of **HB-EGF** from RASMC. However, platelet-derived **growth factor**, another known **growth factor** of smooth muscle cells (SMC), was not induced by both dicarbonyls. The dicarbonyl augmented intracellular peroxides prior to the induction of **HB-EGF** mRNA as judged the flow cytometric anal. using 2',7'**-dichlorofluorescin** diacetate. N-Acetyl-L-cysteine and aminoguanidine suppressed both dicarbonyl-increased **HB-EGF** mRNA and intracellular peroxide levels in RASMC. .delta..lambda.-Buthionine-(S,R)-sulfoximine increased the levels of 3-DG-induced **HB-EGF** mRNA. Furthermore, hydrogen peroxide alone also induced **HB-EGF** mRNA in RASMC. These results indicate that MG and 3-DG induce **HB-EGF** by increasing the intracellular peroxide levels. In addn., the pretreatment with 12-O-tetradecanoylphorbol-13-acetate failed to alter dicarbonyl-induced **HB-EGF** mRNA expression in RASMC, suggesting that the signal transducing mechanism is not mediated by **protein** kinase C. Since **HB-EGF** is known as a potent mitogen for smooth muscle cells and is abundant in atherosclerotic plaques, the induction of **HB-EGF** by MG and 3-DG, as well as the concomitant increment of intracellular peroxides, may trigger atherogenesis during diabetes.
IT **154531-34-7, Heparin-binding epidermal growth factor-like growth factor**
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(**heparin-binding epidermal growth factor-like growth factor** induction by methylglyoxal and 3-deoxyglucosone in aortic smooth muscle cells in relation to diabetic atherogenesis)

L31 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:287535 HCAPLUS
DN 127:1171
TI Lysophosphatidylcholine increases expression of **heparin-binding epidermal growth factor-like growth factor** in human T lymphocytes
AU Nishi, Eiichiro; Kume, Noriaki; Ochi, Hiroshi; Moriwaki, Hideaki; Wakatsuki, Yoshio; Higashiyama, Shigeki; Taniguchi, Naoyuki; Kita, Toru
CS Dep. Geriatric Med., Grad. Sch. Med., Kyoto Univ., Kyoto, Japan
SO Circ. Res. (1997), 80(5), 638-644
CODEN: CIRUAL; ISSN: 0009-7330
PB American Heart Association
DT Journal
LA English
AB Atherosclerotic lesions contain substantial nos. of activated T lymphocytes in addn. to monocytes/macrophages. T cell-derived cytokines and **growth factors** may play a role in atherogenesis; however, stimuli responsible for T-cell activation in atherogenesis have not been fully elucidated. In this study, we provide evidence that lysophosphatidylcholine (lyso-PC), a polar phospholipid component increased in atherogenic lipoproteins and atherosclerotic lesions, can upregulate gene expression and secretion of **heparin-binding epidermal growth factor-**

like growth factor (**HB-EGF**
) in cultured T lymphocytes isolated from human peripheral blood. Effects of lyso-PC on T lymphocytes appear to be selective and specific, since lyso-PC also increases **interleukin** (**IL**)-2 receptor expression but does not affect mRNA levels for **IL**-2 or **IL-4**. Lyso-PC-induced upregulation of **HB-EGF** and **IL**-2 receptor mRNA in peripheral T cells is mostly dependent on exogenous **IL**-2 in conditioned medium. The effect of lyso-PC on **HB-EGF** induction was more potent in CD4+ cells than in CD8+ cells, although lyso-PC increases **IL**-2 receptor expression dramatically in both CD4+ cells and CD8+ cells. Lyso-PC similarly increased **HB-EGF** expression in Jurkat cells, a cell line for human CD4+ T lymphocytes. These results in vitro suggest that lyso-PC may be an important stimulus for T cells in atherogenesis in vivo to upregulate **HB-EGF** and that T cell-derived smooth muscle **growth factors** may modulate atherosclerotic progression.

IT **154531-34-7, Heparin-binding epidermal growth factor-like growth factor**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(lysophosphatidylcholine increases **heparin-binding EGF-like growth factor** expression in human T lymphocytes)

L31 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AN 1996:505420 HCAPLUS

DN 125:186916

TI Production of glycosylated **heparin-binding EGF-like growth factor** in HeLa cells using vaccinia virus

AU Davis, Karen M.; Brigstock, David R.; Johnson, Philip R.; Crissman-Combs, Melissa; McCarthy, Diane W.; Dowing, Marc T.; Besner Gail E.

CS Mol., Cellular, Developmental Biol. Program, Ohio State Univ., Columbus, OH, 43205, USA

SO Protein Expression Purif. (1996), 8(1), 57-67
CODEN: PEXPEJ; ISSN: 1046-5928

DT Journal

LA English

AB **Heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**) is a 22-kDa, O-glycosylated **protein**. Because **recombinant** expression systems permitting a detailed anal. of the functional significance of **HB-EGF** glycosylation have not been described, a **recombinant** vaccinia virus designed to express **HB-EGF** was generated by homologous **recombination** of an intermediate plasmid **vector** carrying the **HB-EGF** cDNA and the genome of vaccinia virus and was used to infect HeLa cells. Prodn. of immunoreactive **HB-EGF** was confirmed by **immunofluorescence** and radioimmunopptn. anal. Furthermore, the expressed **protein** was shown to be a secreted, biol. active **protein** by radioreceptor and DNA synthesis assays of HeLa cell conditioned medium. The **recombinant protein** was purified from the conditioned medium using **heparin**-affinity fast **protein** liq. chromatog. followed by C4 reverse-phase high-performance liq. chromatog. (RP-HPLC). SDS-PAGE and Western blotting of the RP-HPLC-purified product showed an immunoreactive **HB-EGF protein** of approx. 22 kDa that was decreased to a 14-kDa **protein** by treatment with O-glycanase. Amino acid sequencing revealed an N-terminus that was characteristic of native, glycosylated **HB-EGF**. Interestingly, a Thr residue

that is a putative site of O-lined glycosylation failed to be resolved. This system provides a valuable method for evaluating the role of glycosylation in **HB-EGF** function(s) as well as addressing other questions concerning **HB-EGF** structure-function relationships.

IT **154531-34-7P, Heparin-binding epidermal growth factor-like growth factor**
RL: BMF (Bioindustrial manufacture); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(glycosylated **heparin-binding EGF-like growth factor** prodn. in HeLa cells using vaccinia virus)

L31 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:748166 HCAPLUS
DN 123:189239
TI Phorbol ester induces the rapid processing of cell surface **heparin-binding EGF-like growth factor**: conversion from juxtacrine to paracrine **growth factor** activity
AU Goishi, Katsutoshi; Higashiyama, Shigeki; Klagsbrun, Michael; Nakano, Norihiko; Umata, Toshiyuki; Ishikawa, Mutsuo; Mekada, Eisuke; Taniguchi, Naoyuki
CS Dep. Biochem., Osaka Univ. Med. Sch., Osaka, 565, Japan
SO Mol. Biol. Cell (1995), 6(8), 967-80
CODEN: MBCEEV; ISSN: 1059-1524
DT Journal
LA English
AB Vero cell **heparin-binding EGF-like growth factor** (**HB-EGF**) is synthesized as a 20-30-kDa membrane-anchored **HB-EGF** precursor (proHB-**EGF**). Localization and processing of proHB-**EGF**, both constitutive and 12-O-tetradecanoylphorbol 13-acetate (TPA)-inducible, was examd. in Vero cells overexpressing **recombinant HB-EGF** (Vero H cells). Flow cytometry and **fluorescence** immunostaining demonstrated that Vero cell proHB-**EGF** is cell surface-assocd. and localized at the interface of cell to cell contacts. Cell surface biotinylation and immunopptn. detected a 20-30-kDa heterogeneous proHB-**EGF** species. Vero H cell surface proHB-**EGF** turned over constitutively with a half-life of 1.5 h. Some of the 20-30-kDa cell surface-assocd. proHB-**EGF** was processed and a 14-kDa species of bioactive **HB-EGF** was released slowly, but most of the proHB-**EGF** was internalized, displaying a diffuse **immunofluorescent** staining pattern and accumulation of proHB-**EGF** in endosomes. Addn. of TPA induced a rapid processing of proHB-**EGF** at a Pro148-Val149 site with a half-life of 7 min. The TPA effect was abrogated by the **protein** kinase C inhibitors, staurosporine and H 7. Kinetic anal. showed that loss of cell surface proHB-**EGF** is maximal at 30 min after addn. of TPA and that proHB-**EGF** is resynthesized and the initial cell surface levels are regained within 12-24 h. Loss of cell surface proHB-**EGF** was concomitant with appearance of 14- and 19-kDa sol. **HB-EGF** species in conditioned medium. Vero H cell-assocd. proHB-**EGF** is a juxtacrine **growth factor** for EP170.7 cells in coculture. Processing of proHB-**EGF** resulted in loss of juxtacrine activity and a simultaneous increase in sol. **HB-EGF** paracrine mitogenic activity. It was concluded that processing regulates **HB-EGF** bioactivity by converting it from a cell-surface juxtacrine **growth factor** to a processed, released sol. paracrine **growth factor**.

IT **154531-34-7, Heparin-binding EGF-**

like growth factor
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(phorbol ester induces rapid processing of cell surface **heparin -binding EGF-like growth factor** with conversion from juxtacrine to paracrine **growth factor** activity)

L31 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:622456 HCAPLUS
DN 123:26276
TI Membrane-anchored **heparin-binding EGF-like growth factor** (**HB-EGF**) and **diphtheria toxin** receptor-associated protein (DRAP27)/CD9 form a complex with integrin .alpha.3.beta.1 at cell-cell contact sites
AU Nakamura, Kuniaki; Iwamoto, Ryo; Mekeda, Eisuke
CS Institute of Life Science, Kurume University, Fukuoka, 830, Japan
SO J. Cell Biol. (1995), 129(6), 1691-705
CODEN: JCLBA3; ISSN: 0021-9525
DT Journal
LA English
AB **Heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**) is a member of the **EGF** family of **growth factors**, which interact with **EGF** receptor to exert mitogenic activity. The membrane-anchored form of **HB-EGF**, proHB-**EGF**, is biol. active, providing mitogenic stimulation to neighboring cells in a juxtacrine mode. ProHB-**EGF** forms a complex with **diphtheria toxin** receptor-assocd. **protein** (DRAP27)/CD9, a tetra membrane-spanning **protein** that upregulates the juxtacrine mitogenic activity of proHB-**EGF**. We explored whether other **proteins** assoc. with DRAP27/CD9 and proHB-**EGF**. Immunopptn. with anti-DRAP27/CD9 resulted in preferential copptn. of integrin .alpha.3.beta.1 from Vero cell, A431 cell and MG63 cell lysates. Anti-integrin .alpha.3 or anti-integrin .beta.1 copptd. DRAP27/CD9 from the same cell lysates. Chem. crosslinking confirmed the phys. assocn. of DRAP27/CD9 and integrin .alpha.3.beta.1. Using Vero-H cells, which overexpress **HB-EGF**, we also demonstrated the assocn. of proHB-**EGF** with DRAP27/CD9 and integrin .alpha.3.beta.1. Moreover, colorization of proHB-**EGF**, DRAP27/CD9, and integrin .alpha.3.beta.1 at cell-cell contact sites was obsd. by double-**immunofluorescence** staining. At cell-cell contact sites, DRAP27/CD9 was highly coincident with .alpha.-catenin and vinculin, suggesting that DRAP27/CD9, proHB-**EGF**, and integrin .alpha.3.beta.1 are colocalized with adherence junction-locating **proteins**. These results indicate that direct interaction of **growth factors** and cell adhesion mols. may control cell proliferation during the cell-cell adhesion process.
IT **154531-34-7**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(membrane-anchored **heparin-binding EGF-like growth factor** (**HB-EGF**) and **diphtheria toxin** receptor-assocd. protein (DRAP27)/CD9 form a complex with integrin .alpha.3.beta.1 at cell-cell contact sites)

L31 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:672962 HCAPLUS
DN 121:272962
TI Biosynthesis and processing by phorbol ester of the cell surface-associated precursor form of **heparin-binding EGF-like growth factor**

AU Raab, Gerhard; Higashiyama, Shigeki; Hetelekidis, Stella; Abraham, Judith A.; Damm, Deborah; Ono, Minoru; Klagsbrun, Michael
CS Harvard Med. Sch., Children's Hospital, Boston, MA, 02115, USA
SO Biochem. Biophys. Res. Commun. (1994), 204(2), 592-7
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB Human MDA MB 231 cells were found to synthesize mostly the cell surface-assocd. precursor form of **heparin-binding EGF-like growth factor** (HB-BGF), a 27-kDa **protein**. Evidence for this form of **HB-EGF** included increased **fluorescence** intensity when cells analyzed by flow cytometry using anti-**HB-EGF** antibodies, lack of **HB-EGF** in conditioned medium, and sensitivity to **diphtheria toxin**, for which **HB-EGF** is the receptor. Phorbol ester treatment of cells resulted, within 30 min, in loss of cell surface 27 kDA **HB-EGF**, lack of interaction with anti-**HB-EGF** antibodies, accumulation of active 21 kDa **HB-EGF** in conditioned medium, and the acquisition of **diphtheria toxin** resistance. It was concluded that cell surface-assocd. **HB-EGF** is the precursor of a bioactive **growth factor**, is biol. active as the receptor for **diphtheria toxin**, and is susceptible to rapid processing.
IT **154531-34-7, Heparin-binding EGF-like growth factor**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(phorbol ester processing of cell surface-assocd. **heparin-binding EGF-like growth factor** as bioactive **growth factor** precursor and **diphtheria toxin** receptor)

L31 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:596814 HCAPLUS
DN 121:196814
TI Analysis of the expression of growth factor, interleukin-1, and lactoferrin genes and the distribution of inflammatory leukocytes in the preimplantation mouse oviduct
AU Dalton, Tim; Kover, Karen; Dey, Sudhansu K.; Andrews, Glen K.
CS Medical Cent., Univ. Kansas, Kansas City, KS, 66160-7421, USA
SO Biol. Reprod. (1994), 51(4), 597-606
CODEN: BIREBV; ISSN: 0006-3363
DT Journal
LA English
AB The oviduct provides the environment in which fertilization of the egg and subsequent development of the preimplantation mouse embryo occurs, but little is known about the oviduct's capacity to produce **growth factors** or cytokines that may influence these preimplantation events. Northern blot anal. and/or immunohistochem. were employed to examine the expression or cellular distribution, resp., of the **growth factors heparin-binding** epidermal-**like growth factor** (**HB-EGF**), transforming **growth factor** (TGF) .alpha., **EGF**, IGF-I, TGF.beta.1, TGF.beta.2, and TGF.beta.3; of estrogen-regulated lactoferrin (LF); and of the cytokines **interleukin** (**IL**)-1.alpha. and **IL**-1.beta. in the mouse oviduct during the preimplantation period (Days 1-**4** [Day 1 = vaginal plug]) and 7 days after ovariectomy. Except for **EGF**, each of the **growth factors** and the LF genes were expressed in the ampulla and isthmus regions of the oviduct throughout the preimplantation period. Prominent immunostaining in secretory epithelial cells was noted for **HB-EGF**,

TGF.alpha., IGF-I, TGF.beta.1, and TGF.beta.2, and LF. Less intense immunostaining in the serosa and/or smooth muscle was also noted for TGF.alpha., IGF-I, and TGF.beta.1. In contrast, intense immunostaining in smooth muscle was noted for TGF.beta.2, and TGF.beta.3 was detected exclusively in smooth muscle cells. The abundance of these mRNAs was relatively const. during the preimplantation period, and ovariectomy did not reduce the levels of these mRNAs. In contrast to these **growth factors**, the cytokine mRNAs examd. (**IL**-1.alpha. and **IL**-1.beta.) were at or below the limits of detection under these exptl. conditions, and inflammatory leukocytes (LF-immunopos. neutrophils, **IL**-1.beta.-immunopos. monocytes/macrophages, or peroxidase-pos. eosinophils) were not detected in the oviduct, but were abundant in the adjacent uterine stroma on Day 1. These studies show that several **growth factors** are synthesized by the mouse oviduct and suggest that ovarian steroids do not play a major role in modulating expression of these genes in the oviduct during the preimplantation period. Furthermore, unlike the uterus on Day 1, the oviduct does not exhibit an inflammatory response to mating.

=> fil wpix
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MOST RECENT DERWENT UPDATE 200230 <200230/DW>
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=> d all abeq tech tot

L70 ANSWER 1 OF 4 WPIX (C) 2002 THOMSON DERWENT
AN **2002-082745** [11] WPIX
DNN **N2002-061698** DNC **C2002-024972**
TI New nucleotide polymorphisms in the human diphtheria toxin receptor, **heparin-binding epidermal growth factor-like growth factor** (DTR) gene, useful for screening or expressing proteins for treating diseases related to DTR activity.
DC B04 D16 T01
IN CHOI, J Y; KLIEM, S E; KOSHY, B; PARKS, K E; STEPHENS, J C
PA (GENA-N) GENAISSANCE PHARM INC
CYC 94
PI WO 2001079233 A2 20011025 (200211)* EN 66p C07H000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC

LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001057057 A 20011030 (200219) C07H000-00
ADT WO 2001079233 A2 WO 2001-US12302 20010416; AU 2001057057 A AU 2001-57057 20010416
FDT AU 2001057057 A Based on WO 200179233
PRAI US 2000-197375P 20000414
IC ICM C07H000-00
AB WO 200179233 A UPAB: 20020215
NOVELTY - An isolated polynucleotide, comprising polymorphisms in the human diphtheria toxin receptor, **heparin-binding epidermal growth factor-like growth factor** (DTR) gene, is new.

DETAILED DESCRIPTION - An isolated polynucleotide, comprising polymorphisms in the human diphtheria toxin receptor, **heparin-binding epidermal growth factor-like growth factor** (DTR) gene, is new. The isolated polynucleotide has:

(a) a nucleotide sequence comprising:

(i) a first nucleotide sequence that is a polymorphic variant of a reference sequence for the DTR gene or its fragment, where the reference sequence comprises a 16488 base pair sequence, fully defined in the specification and the polymorphic variant comprises a DTR isogene defined by a haplotype consisting of haplotypes 1-10 identified in the DTR gene and fully described in the specification; and

(ii) a second nucleotide sequence that is complementary to (i); or

(b) a nucleotide sequence that is a polymorphic variant of a reference sequence for the DTR cDNA or its fragment, where the reference sequence comprises a 627 base pair sequence, fully defined in the specification, and the polymorphic variant comprises the coding sequence of a DTR isogene defined by one of 10 human haplotypes observed in the DTR gene and fully defined in the specification.

INDEPENDENT CLAIMS are also included for the following:

(1) haplotyping the DTR gene of an individual comprising:

(a) determining if the individual has one of the 14 haplotypes observed in the DTR gene fully defined in the specification, or one of the haplotype pairs observed in the DTR gene and described in the specification; or

(b) determining, for one copy of the DTR gene present in the individual, the identity of the nucleotide at one or more polymorphic sites selected from PS1, PS2, PS3, PS4, PS5, PS6, PS7 or PS8;

(2) genotyping the DTR gene of an individual by determining for the two copies of the DTR gene present in the individual, the identity of the nucleotide pair at one or more polymorphic sites selected from PS1, PS2, PS3, PS4, PS5, PS6, PS7 or PS8;

(3) predicting a haplotype pair for the DTR gene of an individual comprising:

(a) identifying a DTR genotype for the individual, where the genotype comprises the nucleotide pair at two or more polymorphic sites comprising PS1-PS8;

(b) enumerating all possible haplotype pairs, which are consistent with the genotype;

(c) comparing the possible haplotype pairs to the data in the genotype and haplotype pairs observed in the DTR gene described in the specification; and

(d) assigning a haplotype pair to the individual that is consistent with the data;

(4) identifying an association between a trait and at least one haplotype or haplotype pair of the DTR gene, which comprises comparing the frequency of the haplotype or haplotype pair in a population exhibiting the trait with the frequency of the haplotype or haplotype pair in a reference population, where the haplotype comprises haplotypes 1-10 observed in the DTR gene and the haplotype pair is selected from the

haplotype pairs cited in the specification, where a higher frequency of the haplotype or haplotype pair in the trait population than in the reference population indicates the trait is associated with the haplotype or haplotype pair;

(5) a composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in the DTR gene at a polymorphic site consisting of PS1-PS19;

(6) a kit for genotyping the DTR gene of an individual comprising a set of oligonucleotides designed to genotype each of PS1-PS19;

(7) recombinant non-human organisms transformed or transfected with the isolated polynucleotide, where the organism expresses a DTR protein encoded by the first nucleotide sequence or expresses an DTR protein encoded by the polymorphic variant sequence;

(8) a computer system for storing and analyzing polymorphism data for the DTR gene, comprising:

(a) a central processing unit (CPU);

(b) a communication interface;

(c) a display device;

(d) an input device; and

(e) a database containing the polymorphism data; and

(9) a genome anthology for the DTR gene, which comprises DTR isogenes defined by one of the haplotypes 1-10 defined in the specification.

USE - The polynucleotide comprising polymorphisms in the DTR gene is useful in studying the expression and function of DTR, and in expressing DTR protein for use in screening candidate drugs to treat diseases related to DTR activity. The methods and haplotypes are useful in improving the efficiency and output of several steps in the drug discovery and development process, including target validation, identifying lead compounds, and early phase clinical trials. These are also useful for designing clinical trials of candidate drugs for treating a specific condition or disease, as well as for screening compounds targeting DTR to treat a specific condition or disease predicted to be associated with DTR activity. The kit and method are useful for determining if an individual has one of the haplotypes or haplotype pairs. The transgenic animals are useful for studying expression of the DTR isogenes in vivo, for in vivo screening and testing of drugs targeted against DTR protein, and for testing the efficacy of therapeutic agents and compounds for tumor **growth**, smooth muscle hyperplasia or atherosclerosis in a biological system.

Dwg.0/3

FS CPI EPI

FA AB; DCN

MC CPI: B04-A08C2E; B04-E01; B04-E02D; B04-E05; B04-E06; B04-F0100E; B04-F0200E; B04-F0700E; B04-P0100E; B11-C08E2; B11-C08E4; B12-K04A3; B12-K04E; B12-K04F; D05-H09; D05-H12B1; D05-H12D1; D05-H12D2; **D05-H14**; D05-H16; D05-H17A4

EPI: T01-J05B4P

TECH UPTX: 20020215

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The determining step comprises identifying the phased sequence of nucleotides present at each of PS1-8 on at least one copy of the individual's DTR gene. It may also involve identifying the phased sequence of nucleotides present at each of PS1-8 on both copies of the individual's DTR gene. The determining step comprises:

(a) isolating from the individual a nucleic acid mixture comprising both copies of the DTR gene or their fragment, which are present in the individual;

(b) amplifying from the nucleic acid mixture a target region containing the selected polymorphic site;

(c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;

(d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of

at least two different terminators of the reaction, where the terminators are complementary to the alternative nucleotides present at the selected polymorphic site; and
(e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
The method also comprises determining for the two copies of the DTR gene present in the individual the identity of the nucleotide pair at each of PS1-8. In particular, haplotyping the DTR gene comprises determining the identity of the nucleotide at PS2. The method may also comprise:
(a) isolating from the individual a nucleic acid sample containing only one of two copies of the DTR gene or their fragment, that are present in the individual;
(b) amplifying from the nucleic acid mixture a target region containing the selected polymorphic site;
(c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
(d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of at least two different terminators of the reaction, where the terminators are complementary to the alternative nucleotides present at the selected polymorphic site; and
(e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
The identified genotype of the individual comprises the nucleotide pair at each of PS1-PS8. In the method of (4), the trait is a clinical response to a drug targeting DTR.
Preferred Composition: The genotyping oligonucleotide is an allele-specific oligonucleotide that specifically hybridizes to an allele of the DTR gene at a region containing the polymorphic site. The allele-specific oligonucleotide comprises a nucleotide sequence consisting of e.g. cccggcgsaa tctcc; gctggggrca tgggg; aggagcaygg gaaaa; cctcctgyat gtaag; gctgtttmtg caaat; tagctccrgg gtgta; atgggctagc tccrg; agaatctaca cccyg; gcaggcaggg cttrt; or taagttttgt gaaya. The genotyping oligonucleotide is a primer-extension oligonucleotide, where the primer extension oligonucleotide comprises a nucleotide sequence comprises: gtgcccggcg; tcaggagatt; tgtgctgggg; ttcccccatg; aggaggagca; ttcttttccc; ctccctcctg; gcacttacat; caggctgttt; gtgatttgca; ggctagctcc; atctacaccc; ggcagggctt; or gttttgtgaa.
Preferred Kit: The kit further comprises oligonucleotides designed to genotype PS2.
Preferred Polynucleotide: The isolated polynucleotide is a DNA molecule and comprises both the first and second nucleotide sequences. It further comprises expression regulatory elements operably linked to the first nucleotide sequence. The first nucleotide sequence is a polymorphic variant of a fragment of the DTR gene. The fragment comprises one or more polymorphisms comprising cytosine at PS1, adenine at PS3, thymine at PS4, thymine at PS5, adenine at PS6, adenine at PS7 and guanine at PS8. The polymorphic variant comprises an additional polymorphism of thymine at PS2.
Preferred Organism: The recombinant organism is a nonhuman transgenic animal.

L70 ANSWER 2 OF 4 WPIX (C) 2002 THOMSON DERWENT
AN 2001-335931 [35] WPIX
DNN N2001-242476 DNC C2001-103839
TI Screening for agents capable of inhibiting a promoter, especially interleukin-4 inducible epsilon promoter involved in immunoglobulin E production, by using diphtheria toxin constructs.
DC B04 D16 S03
IN KINSELLA, T M
PA (RIGE-N) RIGEL PHARM INC
CYC 93
PI WO 2001034806 A2 20010517 (200135)* EN 80p C12N015-12 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001029044 A 20010606 (200152) C12N015-12 <--

ADT WO 2001034806 A2 WO 2000-US31232 20001113; AU 2001029044 A AU 2001-29044 20001113

FDT AU 2001029044 A Based on WO 200134806

PRAI US 1999-165189P 19991112

IC ICM **C12N015-12**
ICS **C07K014-435**; **C07K014-475**; **C12N015-62**; **C12N015-86**; **C12Q001-68**; G01N033-50; **G01N033-533**

AB WO 200134806 A UPAB: 20010625

NOVELTY - Screening for bioactive agents (BA) which inhibit a promoter, comprising combining candidate BA and a cell containing a fusion nucleic acid (NA) having a promoter and NA encoding **heparin-binding epidermal growth factor-like growth factor** (HBEGF), optionally inducing the promoter, introducing diphtheria toxin to the cell and detecting the cell's presence, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition (C) comprising a retroviral vector containing a nucleic acid encoding HBEGF fused to a nucleic acid encoding a **green fluorescent protein** (**GFP**); and

(2) a cell line selected from CA-46 and BJAB, for screening, comprising a fusion nucleic acid, containing an interleukin (IL)-1 inducible epsilon promoter and a nucleic acid encoding HBEGF.

USE - The method is useful for screening bioactive agents capable of inhibiting a promoter of interest, in particular, IL-4 inducible epsilon promoter (claimed), which is involved in immunoglobulin (Ig)E production. An early step in the Ig switch is the production of sterile epsilon -transcripts in response to IL-4. Inhibitors of IgE production prevent the production of IgE and reduce or eliminate an allergic response. In addition to screening for agonists and antagonists of promoters, the diphtheria toxin/HBEGF system is useful in splice junction analysis, to screen for inhibitors of viral infection, RNA transport, agonists and antagonists of translational level regulators and regulators of post-translational levels.

ADVANTAGE - The method is amenable to high-throughput screening strategies so that large number of potential drugs may be screened rapidly and efficiently.

Dwg.0/18

FS CPI EPI

FA AB; DCN

MC CPI: B04-E05; B04-F0100E; **B04-F1100E**; B11-C08E1; B12-K04E; D05-H09; **D05-H12E**; **D05-H14B**
EPI: S03-E14H; S03-E14H4

TECH UPTX: 20010625

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: BA and the cell comprising the fusion NA are combined by introducing an retroviral vector comprising NA encoding BA to the cell. A library of retroviral vectors comprising a library of candidate BAs is added to a population of cells. The retroviral vector further comprises NA encoding a fluorescent label. Preferred Composition: The retroviral vector in (C), comprises an internal ribosome entry site (IRES), 2a site and IL-4 epsilon promoter fused to the nucleic acid encoding HBEGF. **GFP** is derived from Renilla mulleri, Pitilosarcus gurneyi or Aequorea.

L70 ANSWER 3 OF 4 WPIX (C) 2002 THOMSON DERWENT

AN **1999-059041** [05] WPIX
CR 1991-058151 [08]; 1997-033562 [03]; 1997-469495 [43]; 1999-131299 [11]; 2000-135935 [53]; 2000-664558 [64]
DNC **C1999-017264**
TI Screening assay using reporter gene construct - for modulators of genes associated with cardiovascular diseases.
DC B04 D16
IN CASE, C C; FOULKES, J G; LIECHTFRIED, F E; PIELER, C; STEPHENSON, J R
PA (ONCO-N) ONCOGENE SCI INC
CYC 1
PI US 5846720 A 19981208 (199905)* 95p C12Q001-68 <--
ADT US 5846720 A CIP of US 1989-382712 19890718, CIP of US 1990-555196 19900718, CIP of WO 1990-US4021 19900718, Cont of US 1992-832905 19920207, US 1996-700757 19960815
FDT US 5846720 A Cont of US 5580722
PRAI US 1992-832905 19920207; US 1989-382712 19890718; US 1990-555196 19900718; WO 1990-US4021 19900718; US 1996-700757 19960815
IC ICM **C12Q001-68**
ICS C07H021-04; C12N015-85; C12P019-34
AB US 5846720 A UPAB: 20001214
Method for determining if a test compound is capable of specifically transcriptionally modulating the expression of a gene encoding a protein of interest associated with the treatment of cardiovascular disease comprises: (a) contacting a sample containing a predefined number of identical eukaryotic cells with a predetermined concentration of the test compound, where the cells contain a DNA construct consisting of, in 5' to 3' order: a modulatable transcription regulatory sequence of the gene encoding the protein of interest; a promoter of the gene encoding the protein of interest; and a reporter gene under the control of the promoter; (b) measuring the signal produced by the reporter gene or the amount of mRNA transcribed from the reporter gene; and (c) comparing the measurement with that obtained in the absence of the test compound.

USE - The cardiovascular disease may be atherosclerosis or restenosis. The protein of interest may be involved in lipid transport or cellular uptake e.g. apolipoprotein (a, Al, AII, AIV, B, CI, CII, CIII or E), low density lipoprotein receptor (LDL-R), cholesterol ester transfer protein, hepatic TG lipase, lipoprotein lipase, high density lipoprotein receptor p110, LDL receptor **like** protein, ARPl, LDL-R protein kinase, apolipoprotein E receptor or oncostatin M. The protein of interest may be involved in the uptake of modified lipoproteins e.g. LDL-R, scavenger receptor, advanced glycosylated end product receptor or macrophage FC receptor. The protein of interest may be involved in lipid metabolism e.g. AMP-activated protein kinase, AMP activated protein kinase, acetyl CoA cholesterol ester transferase, lecithin cholesterol ester transferase, cholesterol 7 alpha -hydroxylase, hormone sensitive lipase/cholesterol ester hydroxylase or HMG CoA reductase. The protein of interest may be involved in lipid oxidation e.g. 15-lipoxygenase, IL-4, IL-4 receptor, superoxide dismutase or 12-lipoxygenase. The protein of interest may be involved in smooth muscle cell **growth** such as platelet derived **growth factor** (PDGFaA), PDGF-B, PDGF-alpha receptor, PDGF- beta receptor, **heparin-binding EGF-like growth factor**, basic fibroblast **growth factor** (bFGF), aFGF, FGF receptor, IL-1, IL-1 receptor p80, IL-1 receptor protein kinase, interferon gamma, TGF- beta 1, TGF- beta 2, TGF- beta 3, TGF receptor, tumour necrosis **factor** alpha (TNF- alpha), TNF- alpha receptor, alpha -thrombin, alpha -thrombin receptor, 9-hydroxyoctadeca-10,12-dienoic acid (9-HODE) receptor, insulin **like growth factor**, platelet **factor**-4, TGF- alpha , thromboxane A2 receptor, 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) receptor, 13-hydoxyoctadeca-9,11-dienoic acid (13-HODE) receptor, IL 6, IL 6 receptor or **EGF** receptor. The protein of interest may be an endothelial cell **growth factor** or receptor (

EGF) such as vascular **EGF**, VEGF receptor, bFGF, aFGF, FGF receptor or platelet derived endothelial cell **growth factor**. The protein of interest may be associated with macrophage **growth** and chemotaxis e.g. CSF-1, CSF-1 receptor, monocyte chemoattractant protein 1 (MCP-1) or MCP-1 receptor. The protein of interest associated with atherosclerosis may be associated with endothelial cell adhesion such as VCAM-1, VLA-4 alpha 4 subunit, VLA-4 beta 1 subunit, ELAM-1, lCAM-1, LFA-1 alpha L subunit, LFA-1 beta 2 subunit, GMP-140 (PADGEM), neuropeptide Y, VLA-4 alpha 1 subunit, vitronectin receptor or 13-HODE receptor. The protein of interest associated with the treatment of cardiovascular disease or atherosclerosis may be PEPCK. The cardiovascular disease may be associated with thrombosis. In these cases the protein of interest may be one of the following: fibrinogen, fibrinogen receptor subunit IIb, fibrinogen receptor subunit IIIa, fibrinogen receptor subunit beta 3, fibrinogen receptor subunit alpha v, von Willebrand **factor** (vWF), vWF receptor subunit Ib beta , vWF receptor subunit Ib alpha , vWF receptor subunit GPIX, plasminogen activator-1, platelet activating **factor** receptor, plasminogen, tissue plasminogen activator t PA, u-PA, **factor** V, **factor** VII, **factor** VIII, **factor** IX, **factor** X, **factor** XI, **factor** XII, protein C, protein S, thrombomodulin, tissue **factor**, thrombospondin, CD36, kininogen, an eicosanoid receptor or an eicosanoid biosynthetic enzyme. The cardiovascular disease may be hypertension. The protein of interest associated with hypertension includes: angiotensin, preprorenin, renin, angiotensin converting enzyme (ACE), atrial natriuretic peptide (ANP), brain natriuretic peptide, C natriuretic peptide, natriuretic peptide receptor A, natriuretic peptide receptor-B, natriuretic peptide receptor C, EDRF, nitric oxide synthase 1 (Ca+2/calmodulin dependent), nitric oxide synthase II (inducible), nitric oxide dependent guanylate cyclase alpha subunit, nitric oxide dependent guanylate cyclase beta subunit, alpha -adrenoceptors, endothelins, endothelin receptors. vasopressin, vasopressin receptor, serotonin (5-HT) receptors, adenosine receptors, P2 purinoceptors, calcitonin gene related peptide (CGRP), CGRP receptor, substance P, substance K, neurokinin B, tachykinin receptor, angiotensin II receptor AT1, kininogen, tissue kallikrein, plasma kallikrein, an acetylcholine receptor, a voltage dependent calcium channel, an eicosanoid receptor, an eicosanoid biosynthetic enzyme, a beta -adrenoceptor, Na+, K+-ATPase, vasoactive intestinal peptide, a histamine receptor, an aldosterone receptor or heart angiotensinogen kinase. Additional cardiovascular diseases or diseases associated with the symptoms of cardiovascular diseases include congestive heart failure, angina, ischemic heart disease, diabetes mellitus, non-insulin-dependent diabetes, thrombophlebitis, stroke, hypercholesteraemia, familial hypercholesteraemia, combined familial hypercholesteraemia, hyperglycaemia or diseases associated with calcium regulation or metabolism.

Dwg.0/42

FS CPI
FA AB
MC CPI: B04-E03; B04-F02; B04-F0200E; B11-C08E; B12-K04A2; B14-F01; B14-F07; D05-H09; D05-H12

L70 ANSWER 4 OF 4 WPIX (C) 2002 THOMSON DERWENT

AN **1996-209350** [21] WPIX
DNC **C1996-066797**
TI DNA contg. **heparin binding epidermal growth factor-like** enhancer - used to provide endothelial cell specific expression of heterologous protein, partic. for inhibition of arteriosclerosis..
DC B04 D16
IN FEN, Z; LEE, M; ZHOU, F
PA (HARD) HARVARD COLLEGE

CYC 19
PI WO 9610628 A1 19960411 (199621)* EN 38p C12N001-20
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP
US 5656454 A 19970812 (199738) 13p C12N015-00
ADT WO 9610628 A1 WO 1995-US12880 19951004; US 5656454 A US 1994-317333 19941004
PRAI US 1994-317333 19941004
REP 4.Jnl.Ref; US 4764504
IC ICM C12N001-20; C12N015-00
ICS C12N005-10; **C12N015-12**
AB WO 9610628 A UPAB: 19960529
Pure DNA (I) contg. a **heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**) enhancer is new. Also new are: (1) vectors contg. (I); and (2) endothelial cells contg. a vector as in (1).
USE - (I), when associated with a sequence encoding a heterologous polypeptide, is used to inhibit arteriosclerosis (by inhibiting proliferation of smooth muscle cells), or (not claimed) other vascular diseases such as hypertension and excessive blood clotting. Also new is treatment of arteriosclerosis by using a cpd that **binds** to (I). (I) can also be used to direct endothelial-cell specific polypeptide expression and to identify cpds that inhibit expression of **HB-EGF** (from their ability to **bind** to (I)).
Dwg.0/7
FS CPI
FA AB
MC CPI: B04-E03; B04-E08; B04-F0200E; B12-K04; B14-F07; D05-H12D5; D05-H12D6; **D05-H12E**; D05-H14B2; D05-H17
ABEQ US 5656454 A UPAB: 19970922
A substantially pure DNA comprises a **heparin-binding epidermal growth factor-like growth factor** (**HB-EGF**) enhancer, operably linked to a heterologous promoter and a sequence encoding a heterologous polypeptide, where the enhancer comprises a 316 base pair sequence given in the specification and the enhancer directs endothelial cell-specific expression of the heterologous polypeptide.
Dwg.0/7

=> d his

(FILE 'HOME' ENTERED AT 14:13:19 ON 14 MAY 2002)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 14:13:33 ON 14 MAY 2002
L1 67 S ?HBEGF?

FILE 'REGISTRY' ENTERED AT 14:13:56 ON 14 MAY 2002
L2 1 S 154531-34-7

FILE 'HCAPLUS' ENTERED AT 14:14:38 ON 14 MAY 2002
L3 375 S L2
L4 517 S HEPARIN(L)BIND?(L)(EGF OR EPIDERMAL GROWTH FACTOR)(L)LIKE(L)G
L5 389 S HB EGF
L6 601 S L1,L3-L5
L7 9063 S GREEN(L)?FLUORESC?(L)PROTEIN OR GFP
L8 1 S L6 AND L7
L9 9 S ?FLUORESC?(L)PROTEIN AND L6
L10 1 S GREEN(L)?FLUORESC? AND L6
L11 8 S L9,L10 NOT L8

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L12          1364 S IRES OR INTERNAL?(L)RIBOSOM?(L)ENTRY?(L)SITE
L13         17084 S (IL OR INTERLEUKIN)()4
L14         31932 S (IL OR INTERLEUKIN)(L)4
L15             1 S L6 AND L12
L16             8 S L6 AND L13
L17            11 S L6 AND L14
L18             1 S L15-L17 AND EPSILON
L19             1 S L8,L10,L15,L18
L20            18 S L8-L11,L15-L19 NOT L19
L21            11 S L20 AND (RECOMBIN? OR ?DIPHTHER? OR ?TOXIN? OR ?TOXOID? OR VE
L22             7 S L20 NOT L21
                  E KINSELLA T/AU
L23             8 S E14,E15
L24             1 S L23 AND L6
L25             1 S L19,L24
                  E RIGEL/PA,CS
L26             1 S E3-E13 AND L6
L27             1 S L25,L26
L28             1 S L27 AND L1,L2-L27
L29             0 S LL20-L22 NOT L28
L30            18 S L20-L22,L11 NOT L28
L31            18 S L30 AND L1,L2-L30

     FILE 'REGISTRY' ENTERED AT 14:44:55 ON 14 MAY 2002

     FILE 'HCAPLUS' ENTERED AT 14:45:09 ON 14 MAY 2002

     FILE 'BIOSIS' ENTERED AT 14:47:02 ON 14 MAY 2002
L32           711 S L6
L33         10326 S L7
L34             0 S L32 AND L33
L35             6 S L12,L13,L14 AND L32
                  E KINSELLA T/AU
L36            58 S E3,E8,E15
L37             0 S L32 AND L36
                  E RIGEL/CS
L38             0 S E3-E21 AND L32
L39             9 S L32 AND ?FLUORESC?(L)PROTEIN
L40             0 S L32 AND ?FLUORESC?(L)GREEN
L41             0 S L32 AND GREEN(L)PROTEIN

     FILE 'MEDLINE' ENTERED AT 14:49:41 ON 14 MAY 2002
L42           512 S L6
L43             0 S L7 AND L42
L44          8248 S L7
                  E LUMINESCENT PROTEINS/CT
                  E E3+ALL
L45          6172 S E4+NT
L46          5526 S E4/BI,CN,CT
L47             0 S L42 AND L45-L46

     FILE 'EMBASE' ENTERED AT 14:51:57 ON 14 MAY 2002
L48           485 S L6
L49          6360 S L7
L50             0 S L48 AND L49

     FILE 'WPIX' ENTERED AT 14:52:58 ON 14 MAY 2002
L51            46 S L4 OR L5
L52           746 S L7
L53             2 S L51 AND L52
L54             1 S L51 AND G01N033-533/IC,ICM,ICS,ICA,ICI
L55             1 S L51 AND C12N015-86/IC,ICM,ICS,ICA,ICI
L56             3 S L51 AND C12N015-62/IC,ICM,ICS,ICA,ICI
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L57           6 S L51 AND C12N015-12/IC,ICM,ICS,ICA,ICI
L58           5 S L51 AND C12Q001-68/IC,ICM,ICS,ICA,ICI
L59           4 S L51 AND C07K014-475/IC,ICM,ICS,ICA,ICI
L60           1 S L51 AND C07K014-435/IC,ICM,ICS,ICA,ICI
L61           4 S L51 AND (B04-F11? OR C04-F11? OR B04-B02B4 OR C04-B02B4)/MC
L62          10 S L51 AND D05-H12E/MC
L63           1 S L51 AND D05-H14B/MC
L64           4 S L51 AND D05-H14/MC
L65          17 S L54-L64
L66           2 S L53 AND L65
L67           1 S L66 NOT APOPTOSIS
L68          15 S L65 NOT L66
                SEL DN AN 4 14  15
L69           3 S E1-E7
L70           4 S L67,L69 AND L51-L69

     FILE 'WPIX' ENTERED AT 15:08:04 ON 14 MAY 2002
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